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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

HL

Office Action Summary	Application No.	Applicant(s)	
	10/044,006	BAGUISI ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-22 and 26-40* is/are pending in the application.

4a) Of the above claim(s) *36-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-22 and 26-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5 and 23-25 have been canceled. Claims 26-40 have been added. Claims 6-22 and 26-40 are pending.

Election/Restrictions

Newly submitted claims 36-40 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the method of claims 36 and 37 do not result in producing an avian comprising a heterologous gene as in claim 6. Claim 36 is directed toward methods of isolating PGCs according to their sex, which may or may not be used for creating avians or for transfection with a heterologous gene. Claim 37 is directed toward producing an egg in which the sex is determined by contacting the egg with a hormone. Claim 37 does not require the egg has an embryo or that the embryo has a heterologous gene. The classification of separating PGCs according to their sex is materially distinct and separate than making avians with heterologous genes and is classified differently. Searching both subjects together would be undue. The classification for contacting an egg with a hormone is materially distinct and separate than making avians with heterologous genes and is classified differently. Searching both subjects together would be undue.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 36-40 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 6-22 and 26-35 are under consideration in the instant office action.

Applicant's arguments filed 12-16-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Oath/Declaration

The copy of the signed oath or declaration has been entered.

Specification

Reference to the US Patent application on pg 17, lines 16, will need updating as necessary.

Claim Rejections - 35 USC § 112

Claims 6-22 remain rejected and claims 26-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 6-22 require producing an avian comprising a heterologous gene and expressing a heterologous gene.

In this case, the only reason to produce an avian comprising a heterologous gene is "to introduce heterologous nucleic acids into the avian genome. The methods are used to improved breed quality, produce avian models of non-avian diseases (e.g.,

human diseases), confer disease resistance to birds, and to produce recombinant proteins for pharmaceutical and other uses." (pg 6, lines 7-13). The "transfected (or transgenic gonadal [sic] PGCs are used to generate germline transgenic chickens" (pg 6, lines 26-27). However, the specification does not provide adequate guidance for one of skill to introducing a nucleic acid molecule into the genome of an avian or to produce germline chimeras carrying the heterologous transgene. The specification does not provide adequate guidance for one of skill to make a avian with improved quality, that is a model of human disease, that is disease resistant or that is a "universal recipient" because these all require introducing a nucleic acid molecule into the genome of an avian. Thus, while the phrase "introducing a nucleic acid molecule into the genome" has been deleted, the claimed invention directed toward producing an avian species comprising a heterologous gene still requires introducing the heterologous nucleic acid sequence into the genome.

The claims require transfecting sex-determined gonadal cells with a nucleic acid molecule prior to being introduced into a recipient embryo. Transfecting avian PGCs cells with a nucleic acid and transplanting the cells into a recipient embryo was known in the art. Stage 11 PGCs had been isolated from chickens, transduced with retrovirus, and immediately injected into the vasculature of Stage 15 chick embryos to obtain germline transmission of a transgene (Vick, Proc. R. Soc. Lond., 1993, Vol. 251, pg 179-182). Although manipulated embryos that hatched were observed to produce offspring of the donor germline, F_1 offspring lost their ability to transmit the donor DNA as they matured (Proudman, 2001, Biotechnology in Animal Husbandry, Vol. 5, pg 283-

299, Renaville and Burny (eds.) Kluwer Academic Publishers; pg 290, 2nd full ¶). Thus, the nucleic acid was not introduced into the genome of the avian; the nucleic acid was introduced episomally. Therefore, it was unpredictable whether transfected gonadal cells with a nucleic acid molecule introduced into a recipient embryo would result in the nucleic acid molecule being introduced into the genome of an avian at the time of filing.

The art did not teach how to make a transgenic avian whose genome comprised a heterologous nucleic acid sequence using transfected avian gonadal cells introduced into recipient avian embryos. For example, Mohammed (1998, Immunotechnology, Vol. 4, pg 115-125) states despite discussions of using hens for the production of recombinant human antibodies (rhAb) and attempts to do so, it had never been demonstrated. Mohammed transfected a lymphoblastoid cell line with a retrovirus encoding a rhAb, injected the cells into a chicken and obtained expression of the rhAb in the egg yolk and sometimes the egg white (pg 116, col. 1, 2nd ¶; col. 2, 1st full ¶). Mohammed did not teach how to obtain the same results using transfected blastodermal cells.

The art taught that avian gonadal cells could not be transfected and cultured over a period of time while maintaining their germline competence.

Ivarie (Trends in Biotechnology, Jan. 2003, Vol. 21, pg 14-19) taught that the complex process by which a bird makes and lays eggs makes the production of transgenic birds materially distinct and separate from those of mice. Ivarie cites Pain and teaches cultured, non-transfected, stage X blastodermal cells provided germline transmission; however, the cultured, transfected, stage X blastodermal cells did not

maintain their germline competence. No transgenic birds have been made using cultured, transfected stage X blastodermal cells. The biggest obstacle to overcome in making transgenic birds whose genomes' comprise an exogenous transgene using transfected embryonic gonadal cells is the loss of germline competence during culture of transfected gonadal cells (Ivarie, pg 14, col. 2, 3rd full ¶, 1st sentence; pg 17, col. 1, 2nd full ¶, last two sentences; pg 17, sentence bridging col. 1-2; pg 17, col. 2, last sentence). Therefore, transfected avian gonadal cells were known to not maintain their germline competency and could not be used to make transgenic avians whose germ cells comprise the transgene or that expressed a heterologous protein.

While the specification teaches making chimeric chickens, the chimeric chickens were not made with transfected donor gonadal cells (Example 4, pg 19-26, especially pg 20, lines 4-16; Example 5, pg 28, lines 1-11). The specification does not provide the guidance required to overcome the unpredictability in the art for one of skill to determine how to transfect gonadal cells that maintain their germline competency upon being transplanted into a recipient embryo and make transgenic avians having a genome comprising the transgene. Nor does the specification provide any working examples of making transgenic avians using transfected gonadal cells as claimed. Therefore, the specification does not overcome the unpredictability in the art at the time of filing. It would have required one of skill in the art to determine the parameters required to transfect gonadal cells such that a transgenic avian having a genome with the transgene as claimed would be produced as opposed to maintaining the transgene episomally as shown by Li (cited above).

Applicants argue the "heterologous nucleic acid need not be integrated into the genome in order to improve the quality of an animal, confer disease resistance, or to serve as a model for human disease." Applicants' argument is spurious and is not supported by any evidence. In fact, it is contrary to the teachings in the specification on pg 6, lines 7-13, which requires incorporation of the gene into the genome. Furthermore, pg 6, lines 26 and 27, teach the heterologous nucleic acid is incorporated into the germline (the heterologous nucleic acid sequence must be incorporated into the genome to be passed through gametes to other generations). Thus, the claimed invention is limited to avians whose genomes comprise the heterologous nucleic acid sequence.

Applicants argue Proudman enables obtaining an avian whose genome comprises a heterologous gene because "Proudman even cites Vick stating that transfected PGCS can successfully be used to produce transgenic offspring." Applicants' argument is not persuasive. Proudman taught the heterologous nucleic acid sequence of Vick was passed on to offspring of the founder chimeric chicken; however, Proudman taught F_1 offspring lost their ability to transmit the donor DNA as they matured (pg 290, 2nd full ¶). Thus, Proudman taught the heterologous nucleic acid was introduced episomally and not introduced into the genome of the avian. Therefore, it was unpredictable whether transfected gonadal cells with a heterologous nucleic acid molecule introduced into a recipient embryo would result in the nucleic acid molecule being introduced into the genome of an avian at the time of filing.

Applicants state they are not clear why Mohamed is relevant to the claimed invention (pg 9 of response, line 2). Mohamed was used to establish that the desire to make transgenic avians expressing antibodies existed at the time of filing. Mohamed established that transgenics expressing antibodies had only been done by transfecting a lymphoblastoid cell line with a retrovirus encoding a rhAb, injected the cells into a chicken and obtaining expression of the rhAb in the egg yolk and sometimes the egg white. Mohamed did not teach incorporating the heterologous gene into the genome of the avian.

Applicants point to the examples on pg 16, lines 25, through pg 17, line 2, and pg 20, lines 17-25. None of the examples show the heterologous sequence was transmitted through the germline. In particular, pg 20, lines 17-25, merely teaches the donor PGCs were passed through the germline and does not teach the donor PGCs were stably transfected, i.e. maintained the heterologous nucleic acid sequence in the genome, in the F1 offspring.

The declaration by Paul DiTullio has been considered and is not persuasive. The declaration does not teach the heterologous nucleic acid sequence was incorporated into the genome of the sperm of the chimeric chicken. As such, the declaration does not enable one of skill to obtain a transgenic avian capable of stably passing the heterologous nucleic acid sequence onto its offspring through the genome. Merely expressing the nucleic acid sequence in sperm of the chimera does not guarantee the nucleic acid sequence will be passed on to the offspring or that the nucleic acid sequence is incorporated into the genome of the sperm cell.

Claims 6-22 remain rejected and claims 26-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 6 as newly amended is indefinite because the metes and bounds of what applicants consider "isolated sex-determined gonadal cells" cannot be determined. It is unclear whether the phrase encompasses PGCs that have either have two X chromosomes (female) or one X and one Y chromosome (male) capable of determining the sex of the PGCs. It is unclear if the phrase limits the cells to those isolated after a particular stage of development. It is unclear if the phrase limits the cells to those isolated after a particular stage of development and tested to determine which sex the cells are differentiating into. The term is not defined in the specification and does not have an art recognized meaning. Therefore, those of skill could not determine when they were infringing on the claim.

In claim 6, the scope of the preamble is not commensurate with the body of the claim. The preamble requires producing an avian comprising a heterologous gene but the body of the claim requires producing an avian that expresses the heterologous gene. It is unclear if the avian must merely comprise the heterologous gene or if the avian must comprise the heterologous gene and express the heterologous gene.

Claim 6 is indefinite because it uses the phrase "heterologous gene" in the preamble and the last phrase in the body of the claim, but merely requires "transfecting said population with a heterologous nucleic acid molecule" in step b of the claim. It is

unclear if the heterologous nucleic acid is the same as the heterologous gene or if the two differ in some way.

The metes and bounds of when a population of isolated gonadal cells comprises at least 0.5%, 1%, 50% or 90% primordial germ cells (PGCs) (claims 7-10) cannot be determined. It is unclear what criteria applicants use to define PGCs. More importantly, it is unclear if the percentage of PGCs must occur during the isolation process (i.e. a particular stage in which the percentage of PGCs is increased in the embryonic gonad) or when the gonadal cells are transferred into the recipient embryo (i.e. after PGCs have been preferentially cultured or separated from non-PGCs).

Applicants argue the criteria for PGCs is defined in the specification on pg 10, lines 1-6, and was known in the art. Applicants' argument is not persuasive. Pg 10, lines 1-6, states, "The PGCs can be transfected together with the other gonadal stromal cells or isolated prior to transfection using a ficoll density gradient (Yasuda et al, 1992, J. Reprod. Fert. 96: 521-528). Further purification is accomplished by short-term culture (15-30 minutes) of the isolated cells. The gonadal stromal cells attach more rapidly to plastic, e.g., a tissue culture plate, than the PGCs, thus allowing purification of gonadal PGCs to approximately 90% or higher." Pg 10, lines 1-6, does not describe how the percentage of PGCs were determined or define the metes and bounds of PGCs. Nor does the specification teach how much more rapidly stromal cells attach to plastic than PGCs. Overall, the specification does not provide adequate guidance for one of skill to determine how long or how many tissue flasks are required to obtain any specific percentage of PGCs in a tissue culture flask. As such, one of skill would not be able to

determine if they had infringed upon the claimed invention using the specification. Yasuda (1992) taught isolating PGCs but did not differentiate PGCs and non-PGCs so that the percentage of PGCs in a cell population could be determined. It is noted that the description on pg 10, lines 1-6 is not the same as the method described by Yasuda; therefore, one of skill would not have known whether they were infringing on the claimed invention because they would not have known which method to use to determine the percentage of PGCs in a cell population. While populations of cells comprising PGCs were known in the art, the art did not have one method for determining the percentage of PGCs in a cell population.

In claims 11, 12, 15 and 16, the staging of embryos is unclear. Applicants argue the Hamburger & Hamilton (H & H) method of staging is being used. However, the specification uses incorrect days to describe the stages.

Pg 9, line 10, describes stage 31-34 as day 7-8 after incubation (after being layed), which is correct (H & H, 1951, J. Morph. Vol. 88, pg 49-92. see pg 62-63).

Pg 2, lines 14-15, describe stage 29-36 as day 7.5, which H & H describe stage 29-36 as 6-10 days.

Pg 11, line 9, describes stage 7-8 as 24 hours, which H & H describes stage 7-8 as 23-29 hours; 24 hours does not include stage 8 according to H & H (H & H pg 55).

Pg 11, line 11, describes stage 11-13 as 48 hours, while H & H describes stage 11-13 as 40-49 hours. Stage 11 does not include 48 hours according to H & H (pg 55). Pg 2, lines 23-24, pg 11, line 14, pg 11, lines 17-19, pg 11, lines 20-21 and pg 11, line 25, regarding the H & H method of staging.

Because of the difference in the description of staging in the specification as compared to the H & H method, it cannot be determine whether applicants are attempting to redefine the stages or if the specification has errors. As such, reference to stages in claims 11, 12, 15 and 16 is unclear. One of skill would not been able to determine whether applicants were attempting to be their own lexicographer or whether the description of the stages was in error. Applicants have not addressed whether applicants are attempting to redefine the H&H system or if the of staging or whether the specification has numerous errors.

The rejection regarding "derived" in claims 13 and 14 has been withdrawn because the term has been deleted.

The rejection regarding "fertilized avian egg" in claims 15, 16, 18, 19 and 20 lacking antecedent basis in claim 6 has been withdrawn in view of the amendment.

The indefiniteness rejection of claims 19-21 has been withdrawn because of the amendment.

However, as newly amended claims 19-21 are rejected because "said selected cells" lacks antecedent basis.

Claims 6-22 and 26-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phase "sex-determined gonads" in claim 6 does not have support in the specification as originally filed. Pg 4, lines 8-14, states "Donor PGCs are obtained from sex differentiated gonads and are therefore segregated by sex. Donor PGCs stocks are sex-matched with the recipient egg. Such a strategy insures favorable fertility rates and high germline expression of the donor PGCs (transfected or untransfected). The sex of the recipient egg is hormonally controlled, e.g., by introducing testerone [sic] into the egg to generate a male chick or by introducing estrogen or follicle stimulating hormone into the egg to generate a female chick." Pg 5, lines 4-5 refer to "[a]n isolated population of sex-determined PGCs, e.g., a population of male gonadal PGCs or a population of female gonadal PGCs, is also within the invention." Pg 9, lines 8-9, teaches harvesting eggs at stage 29-36. "The gonads were grouped by sex and dispersed by standard trypsinization procedure and cultured in tissue culture plates until they attach. Sex selection is carried out at the time of collection of the gonadal PGCs prior to transfer of the cells into a recipient egg" (pg 9, lines 16-19). Pg 13, lines 20-22, teaches "At 7-7.5 days of incubation, developmental differences between the differentiating female and the male gonads can be identified allowing for sex selection." Thus, the specification contemplates isolating gonads after Stage 29 and separating the gonads by sex. The specification contemplates controlling the sex of the embryo using hormones. However, the specification does not contemplate the genus of "sex-determined gonads." It cannot be determined when the sex of the gonads has been "determined." Therefore, the phrase "sex-determined gonads" is new matter.

The phrase "heterologous nucleic acid molecule" in claim 6 is new matter. Support for this phrase cannot be found on page 4, lines 8-14, page 5, lines 4-10, page 9, lines 16-19, page 13, lines 20-27, page 25, lines 4-5, or page 27, lines 4-10, as asserted by applicants.

Claims 26-35 are new matter. Support for the limitations cannot be found on pg 4, lines 8-14, page 5, lines 4-10, page 9, lines 16-19, page 13, lines 20-27, page 25, lines 4-5, and page 27, lines 4-10. Applicants state, "[s]upport for new claims 26-29 is found, for example, at page and support for new claims 30-32 is found, for example, at page [sic]" (pg 7, lines 1-3, of response). No support for the new claims has been provided.

Claim Rejections - 35 USC § 102

Claims 6-12, 15, 16 and 22 remain rejected and claims 33 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Petitte (US Patent 6,333,192, filed Aug. 9, 1999) and supported by Hamburger (1951, J. Morphol. Vol. 88, pg 49-92) for reasons of record.

Petitte taught isolating PGCs and stromal cells from the gonads of stage 30 avian embryos, transfecting the PGCs in vitro with a heterologous nucleic acid sequence, and transferring the PGCs into a recipient avian embryo (col. 7, lines 18-38; col. 4, lines 57-67). The avian is incubated to hatch (col. 7, lines 43-45) and the heterologous nucleic acid sequence is expressed (col. 7, line 40). The percentage of PGCs at day 0 was 100% (Figure 1). The recipient avian embryos are implanted with the PGCs prior to 2 or

3 of incubation, and preferably prior to day 1 of incubation (col. 7, lines 36-40). Day 1 (24 hours) of incubation is equivalent to H & H stage 7 as claimed (see pg 55 of Hamburger). Day 2 (48 hours) of incubation is equivalent to H & H stage 13 as claimed (see pg 56 of Hamburger). Inherently, 50% of the recipient embryos were of the same sex as the donor PGCs (claim 22). The PGCs were "sex-determined" as claimed because they either have two X chromosomes (female) or one X and one Y chromosome (male). The PGCs were also "sex-determined" as claimed because they were isolated from the gonads of stage 30 avian embryos after sex differentiation has begun. The PGCs were also "sex-determined" as claimed because stage 30 is greater than stage 27 (claims 11) and at a stage of 29-36 (claim 12).

Claims 6-10, 16, 21 and 22 remain rejected and claims 33 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Tsai (US Patent 6,140,118, filed 8-11-99) for reasons of record.

Tsai taught isolating blastodermal cells from the area pellucida of gonads of Stage IX-XIV avian embryos, transfecting the blastodermal cells with a heterologous nucleic acid sequence, and transplanting the blastodermal cells into a recipient avian embryo that was incubated for 18 hours. The embryos hatched and expressed the heterologous nucleic acid sequence (col. 5, lines 17-20, col. 6, lines 18-19, 39-50; col. 7, lines 9-13; col. 8, lines 10-18). The percentage of PGCs in the blastodermal cells isolated or in the blastodermal cells transplanted into the recipient embryo cannot be determined by the patent office. Since the patent office does not have the ability to

determine the percentage of PGCs in the population of cells isolated or the cells transplanted, without evidence to the contrary, the percentage was at least 90% as claimed because they were grown to confluency and separated from adherent cells (col. 5, lines 43-48). Inherently, 50% of the recipient embryos were of the same sex as the donor PGCs (claim 22). The PGCs were "sex-determined" as claimed because they either have two X chromosomes (female) or one X and one Y chromosome (male) capable of determining the sex of the PGCs. The PGCs were also "sex-determined" as claimed because they were isolated from the gonads of stage IX-XIV avian embryos after sex differentiation has begun.

Claims 6-13, 16, 17 and 22 remain rejected and claims 33 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Hong (Transgenic Res. 1998, Vol. 7, pg 247-252) for reasons of record.

Hong taught isolating PGCs from stage 29 (H & H) White Leghorn embryos, transfecting them with a heterologous nucleic acid sequence and injecting them into day 2.5 (stage 17 H & H) embryos. The eggs were incubated under conditions that allowed development and hatching of the eggs. The embryos expressed the heterologous nucleic acid sequence (see materials and methods and pg 250, col. 1, lines 1-5). Inherently, 50% of the recipient embryos were of the same sex as the donor PGCs (claim 22). The PGCs were "sex-determined" as claimed because they either have two X chromosomes (female) or one X and one Y chromosome (male) capable of determining the sex of the PGCs. The PGCs were also "sex-determined" as claimed

because they were isolated from the gonads of stage 29 avian embryos after sex differentiation has begun. The PGCs were also "sex-determined" as claimed because stage 29 is greater than stage 27 (claims 11) and is equivalent to a stage of 29-36 (claim 12).

Claims 6-10, 13, 16-18 and 22 remain rejected and claims 33 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Vick (Proc. R. Soc. Lond. 1993, Vol. 251, pg 179-182) for reasons of record.

Vick taught isolating primordial germ cells (PGCs) from the germinal crescent cells of a stage 11 White Leghorn chicken embryo, transfecting the cells with a retroviral vector and transplanting the cells into a stage 15 Rhode Island Red chicken embryo. The embryos were incubated until hatch and expressed the retroviral LacZ gene. While Vick taught the mean number of PGCs per germinal crescent was 98 (pg 180, col. 2, line 3-4), Vick did not teach the percentage of PGCs in the population of cells isolated from the germinal crescent. However, the percentage of PGCs in the population of cells isolated from the germinal crescent taught by Vick was inherently at least 90% as claimed (claim 10). Vick taught separating the PGCs from other cells such as yolk cells by centrifugation (pg 180, col. 1, lines 6-8). Vick stated the "PGCs were cultured" and does not state other cell types were included. It is noted that the PGCs' viability was determined throughout the isolation process (pg 180, Table 1 and Figure 1); however, this data does not relate to the percentage of PGCs in the cells isolated from the embryo as claimed. Since the patent office does not have the ability to determine the

percentage of PGCs in the population of cells isolated from the germinal crescent, without evidence to the contrary, the percentage was at least 90% as claimed because Vick taught separating PGCs from yolk cells by centrifugation and specifically refers to culturing PGCs without referring to contaminating cells. Inherently, 50% of the recipient embryos were of the same sex as the donor PGCs (claim 22). The PGCs were "sex-determined" as claimed because they either have two X chromosomes (female) or one X and one Y chromosome (male) capable of determining the sex of the PGCs. The PGCs were also "sex-determined" as claimed because they were isolated from the gonads of stage 11 avian embryos after sex differentiation has begun.

Claim Rejections - 35 USC § 103

Claims 6, 14, 19 and 22 remain rejected and claims 33 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pardue (US Patent 6,354,242, filed 3-23-00) in view of Petitte (US Patent 6,333,192, filed Aug. 9, 1999) for reasons of record.

Pardue taught isolating germ cells from the gonads of stage 27-28 turkey embryos, and transplanting the germ cells into a recipient chicken embryo (col. 6, lines 41-51). The recipient embryos could be optionally sterilized prior to transplantation (col. 1, line 53-55). The embryos were incubated until hatch. Inherently, 50% of the recipient embryos were of the same sex as the donor germ cells (claim 22). The PGCs were "sex-determined" as claimed because they either have two X chromosomes (female) or one X and one Y chromosome (male) capable of determining the sex of the PGCs. The PGCs were also "sex-determined" as claimed because they were isolated

from the gonads of stage 27-28 avian embryos after sex differentiation has begun. Pardue did not teach transfecting the germ cells with a heterologous nucleic acid sequence.

However, Petitte taught isolating PGCs and stromal cells from the gonads of stage 27-28 avian embryos, transfecting the PGCs in vitro with heterologous nucleic acid sequence, transplanting the PGCs into a recipient avian embryo, incubating the embryos until hatch and expressing the heterologous nucleic acid sequence (col. 7, lines 18-42; col. 4, lines 57-67).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate germ cells from the gonad of a turkey embryo and transplant the germ cells into a chicken embryo as taught by Pardue, wherein the turkey germ cells were transfected prior to transplantation as taught by Petitte. One of ordinary skill in the art at the time the invention was made would have been motivated to transfect the turkey germ cells with a nucleic acid sequence encoding a marker protein prior to transplantation into a chicken embryo to detect the turkey cells in the chimeric embryo.

Applicants argue Petite and Pardue do not mention sex-determined PGCs. Applicants' argument is not persuasive. Both the PGCs of Pardue and Petite are "sex-determined" as claimed because they either have two X chromosomes (female) or one X and one Y chromosome (male) capable of determining the sex of the PGCs. The PGCs were also "sex-determined" as claimed because they were isolated from the gonads of stage 27-28 avian embryos after sex differentiation has begun.

Claims 6, 14, 19, 20 and 22 remain rejected and claims 33 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pardue (US Patent 6,354,242, filed 3-23-00) in view of Petitte (US Patent 6,333,192, filed Aug. 9, 1999) as applied to claims 6, 14, 19 and 22 and further in view of Aige-Gil (1991, Res. Vet. Sci. Vol. 50, pg 139-144) for reasons of record.

The combined teachings of Pardue and Petitte taught isolating germ cells from the gonads of stage 27-28 turkey embryos, transfecting the germ cells with a heterologous nucleic acid sequence, sterilizing the recipient embryo prior to transplantation and transplanting the germ cells into the recipient chicken embryo (Pardue, col. 6, lines 41-51; col. 1, line 53-55; Petitte, col. 7, lines 18-42; col. 4, lines 57-67). The combined teachings of Pardue and Petitte did not teach sterilizing the recipient embryo with busulphan.

However, Aige-Gil taught busulphan sterilized avian the PGCs of avian embryos (pg 143, Table 3).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate germ cells from the gonad of a turkey embryo, transfect the turkey germ cells, sterilize a recipient chicken embryo and transplant the germ cells into the chicken embryo as taught by the combined teachings of Pardue and Petitte, wherein the recipient chicken embryo is sterilized using busulphan as taught by Aige-Gil. One of ordinary skill in the art at the time the invention was made would have been motivated to sterilized the recipient embryo with busulphan as taught by Aige-Gil

instead of ultraviolet light as taught by Pardue because Aige-Gil states busulphan provides the advantage of acting predominantly on stem cells while ultraviolet light would act generically on all cells in the embryo.

Applicants argue Petite and Pardue do not mention sex-determined PGCs. Applicants' argument is not persuasive. Both the PGCs of Pardue and Petite are "sex-determined" as claimed because they either have two X chromosomes (female) or one X and one Y chromosome (male) capable of determining the sex of the PGCs. The PGCs were also "sex-determined" as claimed because they were isolated from the gonads of stage 27-28 avian embryos after sex differentiation has begun.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER